

Nucleophilic Substitution in 3-Methoxy-4-hydroxybenzyl Alcohol and 3,4-Dimethoxybenzyl Alcohol

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The kinetics of the reactions between mercaptoacetic acid and two alcohols, namely 3-methoxy-4-hydroxybenzyl alcohol and 3,4-dimethoxybenzyl alcohol, have been studied. The suggestion that nucleophilic substitution of 3-methoxy-4-hydroxybenzyl alcohol occurs *via* the methylene quinone has been further confirmed for aqueous solutions of pH 5. In acidic aqueous solutions a direct S_N2 reaction is considered as an alternative to this two-step process. A S_N2 mechanism is suggested also for the substitution of 3,4-dimethoxybenzyl alcohol.

The aliphatic hydroxyl group of *p*- or *o*-hydroxybenzyl alcohols is easily substituted by a suitable nucleophile *e.g.* an alcohol, a thiol, sulphite or thiosulphate. That methylene quinones are intermediates in this type of reaction has been discussed already by Zincke and Hahn.¹ Their assumption has been supported by recent studies^{2,3} in which simple methylene quinones have been synthesised from 2-hydroxybenzyl alcohols and from 4-hydroxy-3,5-dimethylbenzyl alcohol.

Following an investigation of the reaction of vanillyl alcohol (I) (3-methoxy-4-hydroxybenzyl alcohol) with sulphite, Ivnäs and Lindberg⁴ suggested that these substitutions occur through a two-step mechanism. In the first step, the methylene quinone (II) is formed by a reversible reaction, which is acid-base catalysed. In the second, the intermediate reacts with the nucleophile to yield the substitution product (III). At pH 5 the formation of the methylene quinone is assumed to be slow compared to the second step. The former reaction is then the rate determining step. In more acidic solutions or in basic solutions the reaction of the nucleophile with the intermediate is the rate determining step.

Studies of the reaction of vanillyl alcohol with thiosulphate⁵ and of the hydrolysis of methyl vanillyl ether⁶ have indicated that they also follow this mechanism.

Table 1. Rate constants for the reaction between veratryl alcohol and mercaptoacetic acid.

pH	Temp. °C	$k_I \times 10^3 \text{ min}^{-1}$ Starting concn.		$k_{II} \times 10^2 (\text{min} \times \text{mole/l})^{-1}$ Starting concn.		
		100/50 ^a	100/100 ^b	100/50 ^a	100/100 ^b	
1.80	81.5	4.0→2.8	7.7→3.2	8.3	9.1	
	60.0			1.4		
	44.8			0.26		
2.40	81.5	0.3→0.1	2.0→1.2		2.2	
5.08	136.3			0.5→0.3	0.75	0.73
6.40	136.3			<0.13		<0.1

a) 100 mM of veratryl alcohol and 50 mM of mercaptoacetic acid.

b) 100 mM of veratryl alcohol and 100 mM of mercaptoacetic acid.

This paper describes a kinetic study of the reaction between mercaptoacetic acid and vanillyl alcohol. Veratryl alcohol (3,4-dimethoxybenzyl alcohol) was included in the study because the formation of a methylene quinone is blocked in this case. The choice of these alcohols was also due to our interest in lignin chemistry. The reaction products were characterised as S-(3-methoxy-4-hydroxybenzyl)-mercaptoacetic acid and as S-(3,4-dimethoxybenzyl)-mercaptoacetic acid, respectively. If not otherwise stated the reaction was carried out in aqueous solution.

Veratryl alcohol. As shown in Table 1 the rate of the veratryl alcohol reaction at pH 5 is of first order with respect to both reactants, as the bimolecular rate constant, k_{II} , but not the monomolecular constant, k_I , gives a value which is independent of the reactant concentrations. At pH 1.8–2.4 the reaction product precipitated and this involves uncertainty in the determination of the kinetics. The results in this pH-range indicate, however, bimolecular kinetics as k_{II} is constant. The temperature dependence at pH 1.8 shows that the Arrhenius activation energy is 20 800 cal/mole.

To avoid precipitate formation the reaction was studied in acetic acid-water and in formic acid-dioxane solutions. In both cases complex kinetics were observed certainly due to side reactions.

The rate in aqueous solution is strongly dependent on the acidity. The ratio of the bimolecular rate constant to the hydrogen ion activity, k_{II}/a_{H^+} , at 81.5° is 5.5 for both pH 1.8 and 2.4. The rate is thus proportional to the hydrogen activity. The same ratios calculated for 136.3°C are 3×10^3 and 9×10^3 for pH 1.8 and 4.9, respectively. Even if the extrapolation of the k_{II} at pH 1.8 from the temperature range 44.8–81.5°C to 136.3°C by using the Arrhenius equation involves rather a big degree of uncertainty, we think that this difference is significant. It may be due to the fact that the nucleophile is mostly in the form of mercaptoacetic acid at pH 1.8–2.4 but as its anion at pH 4.9 and the nucleophilicity of the two species may differ. Because of its negative charge, the anion is expected to have the highest nucleophilicity in agreement with the trend in the ratio.

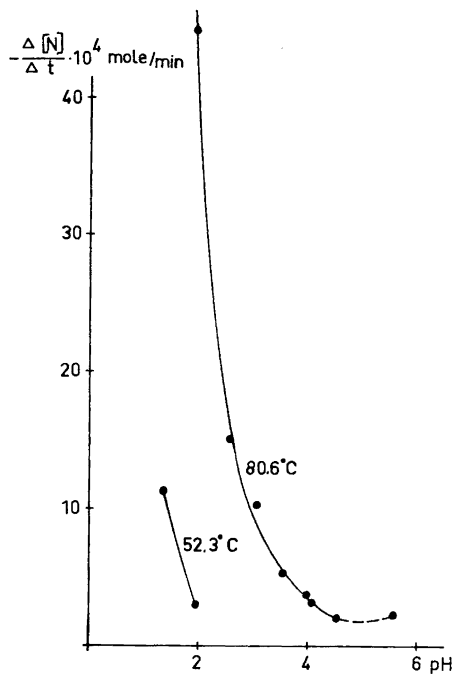
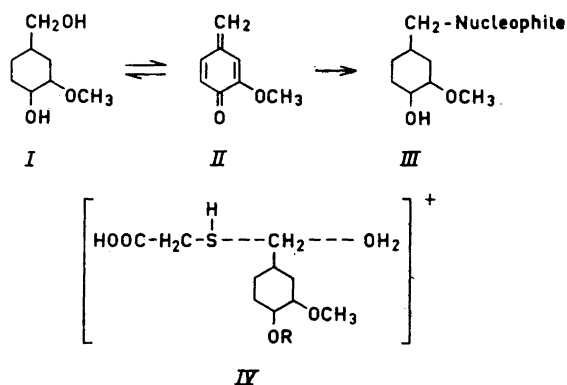


Fig. 1. The instantaneous rate of the reaction between vanillyl alcohol and mercaptoacetic acid. The vanillyl alcohol concentration was 0.2 M and the sum of the concentration of mercaptoacetic acid and that of its anion was 0.1 M.



The simplest and most probable mechanism for bimolecular kinetics is then a S_N2 substitution on the protonised veratryl alcohol. The rate determining reaction should then have the transition state (IV, R = CH₃).

Vanillyl alcohol. The reaction between mercaptoacetic acid and vanillyl alcohol is more complicated than the veratryl alcohol reaction, as could be expected. Fig. 1 shows the rate of this reaction as a function of the acidity. The rate was measured as $-\Delta[N]/\Delta t$, where [N] is the concentration of mercaptoacetic acid (the instantaneous rate). The vanillyl alcohol concentration was 0.1 M and the sum of the concentration of mercaptoacetic acid and that

Table 2. Rate constants for the reaction between vanillyl alcohol and mercaptoacetic acid at pH 5 and 80.6°C.

Expt.	Percentage of dioxane in water	Mercaptoacetic acid reaction				Comparison reactions	
		Starting concn.	u^b	$k_I \times 10^3$ min ⁻¹	$k_{II} \times 10^2$ (min × mole/l) ⁻¹	$k_I \times 10^3$ min ⁻¹ HSO ₃ ⁻	S ₂ O ₃ ²⁻
1	0	50/100 ^a	0.28	2.6	0.36	2.8	2.2- 2.6
2		100/100	0.28	2.7	0.47		
3		100/200	0.38	2.6	1.52		
4	25	100/200	1.38	2.8			
5		100/200		1.1		0.9	
6		100/200		0.36		0.29	
7	50	100/100		0.32			

a) 50 mM of vanillyl alcohol and 100 mM of mercaptoacetic acid.

b) Ionic strength.

of its anion, 0.2 M. As seen, the rate is almost proportional to the hydrogen ion activity in the more acidic solution but at pH 5 it depends only slightly on this activity.

The reaction could not be followed kinetically at higher pH than 6 because there the alcohol was rapidly condensed to di-(4-hydroxy-3-methoxyphenyl)-methane. It was therefore not observed whether the instantaneous rate passes through a minimum at pH 5 as was found in the vanillyl alcohol-bisulphite reaction⁴ and the hydrolysis of vanillyl methyl ether.⁶

The reaction rate at pH 5 is of first order with respect to the vanillyl alcohol concentration but independent of that of mercaptoacetic acid. That follows from Table 2 which shows that in experiments 1–3 and 6–7 the monomolecular constant k_I but not the bimolecular constant k_{II} is independent of the reactant concentration.

The rates at pH 5 are within experimental error equal to the corresponding rates for the bisulphite⁴ and the thiosulphate⁵ reactions (see Table 2). The overall monomolecular kinetics and the identity of rates are in agreement with the mechanism suggested by Ivnäs and Lindberg for the reactions at pH 5 (see introduction).

The distinct difference between the vanillyl alcohol and the veratryl alcohol reactions at pH 5 both in kinetics and in rates is a further indication that the methylene quinone and not the carbonium ion is the intermediate formed in the vanillyl alcohol reaction (*cf.* the discussion by Ivnäs and Lindberg⁴). The rate of the vanillyl alcohol reaction is not affected by the ionic strength (Table 2) which also favours the methylene quinone intermediate as in this case the rate determining step involves neither charge formation nor disappearance. The rate decreases to about one fifth when the aqueous solution is exchanged for a dioxane-water (1:1 v/v) solution and this moderate degree of dependence may be consistent with the above conclusion.

Within the pH range 2.0–2.5 the mercaptoacetic acid reaction is of first order with respect to both reactants, as k_{II} but not k_I (Table 3) gives values

Table 3. Rate constants for the reaction between vanillyl alcohol and mercaptoacetic acid in acid solutions at 44.8°C.

Starting concn.	$k_I \times 10^3 \text{ min}^{-1}$ pH		$k_{II} \times 10^2$ pH	
	2.00	2.46	2.00	2.46
50/100 ^a	1.7	1.0	2.4	1.1
100/100	1.9→1.1	1.1→0.5	2.5	1.3
100/50	1.0 ^b	0.5	3.0 ^b	1.3

a) 50 mM of vanillyl alcohol and 100 mM of mercaptoacetic acid.

b) A precipitate was formed.

c) (Min × mole/l)⁻¹.

which are independent of the reactant concentrations. Here k_{II} is strongly dependent on the acidity.

The simplest explanation for the bimolecular kinetics is of course the same as that for the veratryl alcohol reaction; the reaction is a S_N2 reaction passing over a transition state of the (IV, R = H) type.

Another possibility is that assumed by Ivnäs and Lindberg and mentioned in the introduction. It involves a rapid equilibration of the alcohol with its methylene quinone, which then reacts slowly with the nucleophile. It may be better to assume that in acidic solution the intermediate which reacts with the nucleophile is the carbonium ion. That should explain in a simple way why the reaction is strongly catalysed by hydrogen ion because the amount of carbonium ion in equilibrium with the alcohol is proportional to the hydrogen ion activity.

From our experimental values it is not possible to distinguish with certainty between the S_N2 mechanism and that involving a two-step process. In acid solution the bimolecular rate constant of vanillyl alcohol is about ten times larger than the corresponding constant of veratryl alcohol. This low value may indicate that vanillyl alcohol reacts in the same way as veratryl alcohol does, which is, as mentioned before, probably by the S_N2 mechanism.

EXPERIMENTAL

Kinetic examinations. Samples (5 ml) of a buffer solution containing mercaptoacetic acid and either vanillyl alcohol or veratryl alcohol were heated in glass ampullae, which were flushed with nitrogen while being sealed. The temperature of the heating bath was constant within $\pm 0.1^\circ\text{C}$. After suitable time intervals the ampullae were cooled with ice-water, crushed in water and their contents of mercaptoacetic acid determined by titration with 0.1 N iodine solution. When the reaction was carried out at pH 5 and higher the solution was acidified before titration. The reactions were followed until at least 50 % of one of the reactants was consumed.

The following buffer solutions were used: (a) in the determination of instantaneous rate for vanillyl alcohol at pH 3.5–5.6, mercaptoacetic acid buffers; at pH 2 and below, mercaptoacetic acid-hydrochloric acid solutions; (b) in the determination of the rate constants at pH 5, an acetate buffer. The ionic strength was varied by addition of sodium

chloride; (c) in the determination of the rate constants at pH 2.4 and lower, oxalic acid buffers.

S-(3-Methoxy-4-hydroxybenzyl)-mercaptoacetic acid. A solution of vanillyl alcohol (5 g) and mercaptoacetic acid (7 g) in water (80 ml) was heated for 1 h at 95°C. The solution was extracted with chloroform and the chloroform solution repeatedly shaken with water to remove unreacted mercaptoacetic acid. The chloroform solution was dried and evaporated. The residue was recrystallised from benzene. M.p. 79.5–82.5°C (3.5 g, yield 40 %). [Found: S 14.0; OCH₃ 13.6. Calc. for C₉H₉O₃S(OCH₃): S 13.8; OCH₃ 13.3].

S-(3,4-Dimethoxybenzyl)-mercaptoacetic acid. The compound was obtained from veratryl alcohol in the same way as described above for the corresponding derivative from vanillyl alcohol. The yield of crude product was 68 %. Recrystallisation from benzene gave crystals (yield 38 %) with m.p. 94–96°C. [Found: OCH₃ 25.6; equiv. wt. 246. Calc. for C₉H₉O₃S(OCH₃)₂: OCH₃ 25.6; equiv. wt. 242].

Di-(3-methoxy-4-hydroxyphenyl)-methane. A solution of vanillyl alcohol in aqueous phosphate buffer (pH 7.6) was heated 1/2 h at 80°C. The precipitated oil was collected and dissolved in chloroform. The chloroform solution was dried and poured through a column of silicic acid. The first fraction which passed through gave on evaporation crystals, which were recrystallised from benzene-hexane. The m.p. 101–104°C was in agreement with that published for the diphenylmethane derivative.⁷ (Found: C 68.7; H 6.2; O 24.9. Calc. for C₁₅H₁₆O₄: C 69.3; H 6.2; O 24.6.)

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